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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Applicant's or agent's file reference 31249.CHE.P110PC		Date of mailing (day/month/year) 30.10.2003
IMPORTANT NOTIFICATION		
International application No. PCT/EP02/07657	International filing date (day/month/year) 09.07.2002	Priority date (day/month/year) 09.07.2001
Applicant CHEMOGENIX GMBH		

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Cardenas, C Tel. +31 70 340-3370	
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference 31249.CHE.P110PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP02/07657	International filing date (day/month/year) 09.07.2002	Priority date (day/month/year) 09.07.2001
International Patent Classification (IPC) or both national classification and IPC C07H21/00		
Applicant CHEMOGENIX GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I Basis of the opinion
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 04.02.2003	Date of completion of this report 30.10.2003
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer de Nooy, A Telephone No. +31 70 340-2338



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP02/07657

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-38 as originally filed

Claims, Numbers

1-10 received on 24.09.2003 with letter of 24.09.2003

Drawings, Sheets

1-4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP02/07657

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-10
Industrial applicability (IA)	Yes: Claims	1-10
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP02/07657

Re Item I

Basis of the report

The examination is being carried out on the **following application documents:**

Text for the Contracting States:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR

Description, pages:

1-38 as originally filed

Claims, No.:

1-10 as received on 24/09/2003 with letter of 24/09/2003

Drawings, sheets:

1-4 as originally filed

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Claim 1 is not clear. For examination this claim has been interpreted in the following way: A process for the preparation of polynucleotides in which an oligonucleotide of 2-10 nucleosides with a free 5'-OH group and a 3'-O-protecting group is reacted with a polynucleotide having a 3'-phosphor containing moiety as in claim 1.

2. Reference is made to the following documents:

D1: G. Kumar, M.S. Poonian J. Org. Chem. 49 (1984) 4905-4912
D2: M.C. Pirrung et al. Org. Lett. 3 (2001) 1105-1108

3. Novelty

Document D1 discloses a polynucleotide synthesis where dinucleotides are used containing a 3'-phosphoramidite (phosphite amidoester) and a 5'-O-protecting group which are reacted with an polynucleotide having a free 5'-OH group. Thus, claims 1-10 are novel in the sense of Art. 33(2) PCT.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

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4. Inventive step (claims 1-10)

Document D1, which is considered to represent the most relevant state of the art, discloses a polynucleotide synthesis where dinucleotides are used containing a 3'-phosphoramidite (phosphite amidoester) and a 5'-O-protecting group which are reacted with an polynucleotide having a free 5'-OH group from which the subject-matter of claims 1-10 differs in that instead of the use of an oligonucleotide bearing a 3'-phosphor function as in D1, the oligonucleotide has a free 5'-OH group and the growing chain is bearing the 3'-phosphor function.

The problem to be solved by the present invention may therefore be regarded as the provision of further processes for the synthesis of polynucleotides.

The solution proposed in claims 1-10 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

The interchanging of the phosphor containing moiety from either the growing chain polynucleotide to the building block used for the reaction step, or the other way around, is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. Furthermore, it is generally known to the person skilled in the art that those features can be interchanged where circumstances make it desirable.

Also, the fact that in claim 3 several photolabile protecting groups are named does not make that claim inventive, since those groups are well known, see for instance document D2.

New Patent Claims

1. Process for the preparation of polynucleotides, comprising the step of reacting a selected oligonucleotide of 2 to 10 nucleosides with a phosphite amidoester, phosphotriester or phosphonic ester, which is a 3'-hydroxy group of a free or solid phase bound polynucleotide or a solid phase bound hydroxy group under suitable conditions, characterized in that said selected oligonucleotide has a free 5'-hydroxy group and a terminal 3'-hydroxy group containing a suitable protecting group.
2. Process according to claim 1, characterized in that the selected oligonucleotide is a pentanucleotide, preferably a tetranucleotide, especially preferred a trinucleotide and exceptionally preferred a dinucleotide.
3. Process according to claims 1 or 2, characterized in that the protecting group of the 3'-hydroxy group of the selected oligonucleotide is a photolabile protecting group, preferably a photolabile protecting group selected from the group NPPOC, MeNPOC, NVOC, PyMOC, NBOC, NPES, NPPS.
4. Process according to any one of claims 1 to 3, characterized in that in addition to the selected oligonucleotides, selected and correspondingly derivatized mononucleosides are used.
5. Process according to any one of claims 1 to 4, characterized in that the compounds, which have a hydroxy group derivatized as phosphite amidoester, phosphotriester or phosphonic acid ester, are solid phase bound, wherein the solid phase is selected from the group consisting of silica gel, glass, metal, preferably magnetic metal, plastic, cellulose, dextrane crosslinked with epichlorohydrine, agarose, styrene-divinylbenzene resin, and chloromethylated co-polystyrene-divinylbenzene resin.
6. Process according to claim 5, characterized in that the nucleotides according to any one of claims 1 to 4 are covalently bound to the solid phase via linker molecules.

7. Process according to any one of claims 1 to 6, characterized in that the polynucleotides are DNA- or RNA-nucleotides or polynucleotides made from nucleic acid analogs, such as PNA, LNA or chimeras from these with DNA, RNA or nucleic acid analogs.
8. Process according to any one of claims 1 to 7, characterized in that the steps are performed within an automated process.
9. Process according to claim 8, characterized in that the automated process is designed as parallel synthesis for the creation of a nucleotide library, where the selected oligonucleotides and if necessary some more mononucleotides are selected specifically or at random.
10. Process according to any one of claims 1 to 9 for the preparation of oligonucleotides or nucleic acid chips.